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Original Article

Comparison of Acute Lobar Nephronia and Uncomplicated Urinary Tract Infection in Children

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BACKGROUND/PURPOSE: This aim of this study was to assess the clinical manifestations, the microorganisms involved and their antibiotic resistance in children hospitalized due to acute lobar nephronia (ALN) and non-ALN community-acquired urinary tract infections (UTIs).

METHODS: We retrospectively reviewed the records of 265 previously healthy children hospitalized due to a first-episode of community-acquired febrile UTI between July 2004 and June 2007. Based on the results of renal ultrasonography and computed tomography, they were divided into ALN and non-ALN groups. Their demographic and clinical characteristics, distribution of microorganisms, and their antimicrobial resistance were analyzed.

RESULTS: Of the total number of cases of children admitted with a first-episode community-acquired UTI, 19.2% (n=51) were diagnosed as ALN. Children with ALN were older (1.86 years *vs.* 0.81 years; $p<0.01$), had longer periods of fever before admission (4.7 days *vs.* 1.4 days; $p<0.01$), higher peak body temperatures (39.5°C *vs.* 38.9°C; $p<0.01$), higher white cell counts (18.86×10^9/L *vs.* 15.08×10^9/L; $p<0.01$) and higher C-reactive protein levels (9.0 mg/dL *vs.* 3.5 mg/dL; $p<0.01$) compared with non-ALN children. Fever also persisted for longer after the start of antibiotic treatment in the ALN children (2.7 days *vs.* 1.4 days: $p<0.01$) and they required longer hospital stays and incurred higher medical costs. The major pathogen found in ALN was *E. coli* (90%). The *E. coli* isolated from ALN children was more resistant to cotrimoxazole and ciprofloxacin than those from non-ALN children.

CONCLUSION: ALN is not uncommon in children with a first-episode febrile UTI. They have a prolonged clinical course, higher inflammatory parameters, longer hospital stays and incur higher medical costs. *E. coli* is the major pathogen isolated from these children.

KEYWORDS: acute lobar nephronia, antibiotic resistance, children, community acquired urinary tract infection

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Introduction

Urinary tract infection (UTI) is common in children and is a major reason for referral to emergency rooms and for hospitalization.[1,2] The spectrum of UTIs ranges from uncomplicated lower UTIs to frank abscess formation.[3] Children with acute pyelonephritis (APN) are prone to renal scarring and possible hypertension and chronic renal failure.[4] Acute lobar nephronia (ALN), also known as acute focal bacterial nephritis, is an acute focal bacterial infection

of the kidney without liquefaction.[5] ALN represents an inflammatory upper UTI that lies somewhere between APN and the early stages of renal abscess.[6] A high incidence of urinary tract anomalies is also associated with ALN.[7] The diagnosis of ALN is often delayed due to the nonspecific nature of the symptoms.[8] With the greater understanding of ALN and the use of ultrasound and computed tomography (CT), the condition is now diagnosed more frequently and more quickly in children presenting with UTIs.[9] Longer periods of antibiotic treatment are needed for ALN.[10] *Escherichia coli* is the major pathogen found in the various UTIs, including ALN, and the drug resistance rate is increasing continuously.[6,8,11]

This study reviewed the cases of febrile children hospitalized due to a first episode of community-acquired UTI over a 3-year period in Northern Taiwan. We evaluated the demographic and clinical characteristics, laboratory examinations, imaging studies, causative microorganisms, and their antibiotic resistance and compared the results with those of uncomplicated febrile UTIs. The aims of this study were to find out the prevalence ALN in healthy children hospitalized for UTIs, and to compare ALN with other uncomplicated UTIs.

Methods

Case collection

This retrospective study comprised febrile children (body temperature > 38 °C, and aged < 18 years) with a culture-proven UTI who were hospitalized at the Department of Pediatrics of the National Taiwan University Hospital between July 2004 and June 2007. Using the International Classification of Disease, 9th revision (ICD-9), the medical records of children discharged from hospital with a UTI (code 599.0), APN (code 590.1), and pyelonephritis, unspecified (code 590.80) were reviewed. Only healthy children with a first UTI were enrolled. Children with evident renal abscess, afebrile UTIs, recurrent UTIs, any known urological anomalies, or underlying diseases such as oncologic disorders, neurologic disorders affecting urination, or immunodeficiency were excluded. Children who developed UTI during hospitalization (> 48 hours) or within 48 hours of hospital discharge were also excluded. The demographic characteristics, clinical manifestations and outcomes, laboratory tests, imaging studies, culture results, antimicrobial susceptibilities, and medical costs involved were evaluated retrospectively. Patients were divided into two groups: one with ALN and the other with uncomplicated febrile UTIs (non-ALN). The aforementioned variables were compared for these two groups.

Urine culture and drug sensitivity test

A UTI was identified by urine culture if: at least one microorganism was detected in a urine specimen collected by suprapubic puncture; if $>10^4$ colony-forming units (CFU)/mL were detected in a sample obtained by transurethral catheterization; or $>10^5$ CFU/mL was detected in voided midstream urine or in sterile urine after urine-bag collection.[11–13] UTI was also considered if CT findings suggested ALN, or there were other abnormal findings in the imaging studies, regardless of the results of the urine culture.[14] The identification of microbial growth and the determination of antimicrobial susceptibility was performed using the disk diffusion method according to the guidelines of the Clinical and Laboratory Standards Institute.[15] Ertapenem was substituted for imipenem from September 2005 and ceftazidime for ciprofloxacin from March 2006 according to the laboratory protocol. Empiric antibiotic therapy was defined as inappropriate when the isolated pathogens showed *in vitro* resistance to all the antimicrobial agents used. Generally, antibiotics were shifted from an intravenous to an oral form 2–3 days after defervescence.

Imaging studies

Children admitted with a suspicious UTI underwent renal ultrasonography (RUS), performed by an experienced pediatric nephrologists, within 1–3 days of hospitalization. CT was performed if the RUS revealed unilateral/bilateral nephromegaly, a focal renal mass, or if the patient with borderline nephromegaly remained febrile for 72 hours after the start of antibiotic treatment.[10] A diagnosis of ALN was made based on positive CT findings, or the presence of nephromegaly with or without a focal renal mass.[9,10] The characteristic features of ALN were not visible on the CT scans before contrast medium was injected, but wedge-shaped areas of decreased nephrogenic density were visible after the injection of contrast medium.[3] Unless the parents refused permission to perform voiding cystourethrography (VCUG), the technique was used to

detect vesicoureteral reflux (VUR) in most of the children after their fever subsided. This was not done in some girls older than 5 years of age with a first presentation of UTI.

Statistical analysis

The data were analyzed using SPSS version 15.0 (LEAD Technologies Inc, Illinois, Chicago, USA). Data from the two groups were compared using a χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous variables. A $p < 0.05$ was considered statistical significant.

Results

In total, 265 consecutive, healthy, febrile children with a first-episode community-acquired UTI were identified. Fifty-one children (19.2%) were diagnosed with ALN: all had positive findings on RUS and 40 of them had typical findings on CT scans (i.e. a wedge-shaped decrease in nephrogenic density on injection of contrast medium). The other 214 children (80.8%) were diagnosed with uncomplicated UTIs.

Clinical characteristics of patients

The ages of the children at first presentation ranged from 3 days to 14.7 years, with a median age of 0.31 years; 81.1% were under one year of age. The mean age of the ALN group (1.86 years; range, 23 days to 14.7 years) was older than that of the uncomplicated UTI group (0.81 years; range, 3 days to 10.9 years) ($p < 0.01$; Table 1). The percentage of children less than 3 months old was lower in the ALN group than in the uncomplicated UTI group (13.7% *vs.* 47.2%; $p < 0.01$). Boys predominated in each group, especially at less than 1 year of age. Children with ALN had longer periods of fever and higher peak body temperatures before admission (4.7 days *vs.* 1.4 days; 39.5°C *vs.* 38.9°C, respectively; $p < 0.001$). Children with ALN were also slower to reach defervescence after antibiotic treatment than those without ALN (2.7 days *vs.* 1.4 days; $p < 0.001$). The longest time needed for defervescence after antibiotic treatment in the ALN children was 10 days.

Most of the children in this study were too young to express specific subjective symptoms of UTI such as dysuria, frequency or frank back pain, so these data were only available for some children. Other symptoms, such as poor appetite, diarrhea, nausea and/or vomiting were recorded. The frequency of these symptoms, whether specific or nonspecific for UTI, was low and similar between the two groups.

Most children received empiric antibiotics comprising first generation cephalosporin and/or gentamicin, except for the young infants (< 3 months of age), who received ampicillin and gentamicin empirically. The rate of inappropriate empiric antibiotic treatment was slightly higher in the ALN group than in uncomplicated UTI group (9.8% *vs.* 4.7%; $p > 0.05$). The rates of change for the antibiotics were 33.3% and 37.9% for the ALN and uncomplicated groups, respectively. The reasons for changing antibiotic were: inappropriate antibiotic (23.5% *vs.* 11.1%; $p > 0.05$), remaining febrile after antibiotic use for 2 days (29.49% *vs.* 1.2%; $p < 0.001$), or infection with uropathogens only susceptible to gentamicin (41.2% *vs.* 71.6%; $p < 0.05$). Other reasons included downgrading of the antibiotics, or concomitant medical conditions such as otitis media.

Children with ALN required longer periods of antibiotic therapy, via either intravenous or oral administration (19.1 days *vs.* 10.5 days; $p < 0.05$). Children with ALN also had longer hospital stays (8.6 days *vs.* 6.7days; $p < 0.05$) and higher medical costs (NT$38,927 *vs.* NT$30,369, $p < 0.05$). None of the children with ALN had urosepsis, compared with four children with uncomplicated UTIs. All four episodes of urosepsis were caused by *E. coli*. One child with *E. coli* ALN also suffered from idiopathic thrombocytopenic purpura and was given intravenous immunoglobulin therapy.

Laboratory and imaging studies

All children had blood samples taken and urine analysis on admission. Higher white cell counts were noted in the ALN group (18.86×10^9/L *vs.* 15.08×10^9/L; $p < 0.01$) as well higher neutrophil counts (61.4% *vs.* 52.7%; $p < 0.01$) (Table 2). The inflammatory marker, C-reactive protein, was significantly higher in children with ALN (9.0 mg/dL *vs.* 3.5 mg/dL; $p < 0.01$). The incidence of pyuria was 98.0% in children with ALN compared with 85.5% in children with uncomplicated UTIs ($p < 0.01$). The incidence of hematuria (41.2% *vs.* 34.6%) and positive nitrite tests (29.4% *vs.* 28.5%) was similar in each group.

Of the 51 children with ALN, 20 had left-sided ALN, 12 had right-sided ALN, and 19 had bilateral ALN. RUS and VCUG were performed to identify any genitourinary

Table 1. Comparisons of demographics and clinical manifestations between acute lobar nephronia and non-acute lobar nephronia children[a]

Variable	ALN group (n=51)	non-ALN group (n=214)	p
Age (yr)	1.86±2.77	0.81±1.78	<0.001[c]
Age <1 yr	32 (62.7)	183 (85.5)	<0.001[c]
Age <3 mo	7 (13.7)	101 (47.2)	<0.001[c]
Sex, male	30 (58.8)	138 (64.5)	0.553
<1 yr, male	25 (78.1)	128 (69.9)	0.465
Fever before admission (d)	4.7±6.2	1.4±1.7	<0.001[c]
Peak body temperature (°C)	39.5±0.7	38.9±0.6	<0.001[c]
Symptoms[b]			
Dysuria	4/12	8/12	0.221
Frequency	1/11	2/10	0.929
Flank pain	5/11	6/10	0.819
Poor appetite	12/51	51/214	0.891
Diarrhea	7/51	30/214	0.865
Nausea/vomiting	9/51	26/214	0.417
Time to defervescence (d)	2.7±1.9	1.4±1.2	<0.001[c]
Inappropriate empiric antibiotic	5 (9.8)	10 (4.7)	0.251
Change of antibiotics	17 (33.3)	81 (37.9)	0.645
Inappropriate antibiotics	4 (23.5)	9 (11.1)	0.297
Still febrile 2 days after admission	5 (29.4)	1 (1.2)	<0.001[c]
Susceptible to GM only	7 (41.2)	58 (71.6)	0.029[c]
Others	1 (5.9)	13 (16.0)	0.490
Duration of antibiotics (d)	19.1±3.4	10.5±2.3	<0.001[c]
Intravenous	7.2±3.4	5.1±2.0	<0.001[c]
Oral	12.0±4.3	5.4±2.6	<0.001[c]
Hospital stay (d)	8.6±4.1	6.7±2.3	<0.001[c]
Urosepsis	0 (0)	4 (1.9)	0.730
Medical expense (NT$)	38,927±20,930	30,369±15,640	0.001[c]

[a]Data presented as mean±standard deviation or n (%); [b]data presented as as the nominator of the positive number and the denominator of the number with available records; [c]statistically significant. ALN=acute lobar nephronia; GM=gentamicin; NT$=New Taiwan dollars.

tract anomalies. Forty-two children (82.3%) in the ALN group and 158 children (73.8%) in the uncomplicated UTI group were given a VCUG examination. In all, 22% percent of children were found to have urologic abnormalities and 17% of children given VCUG were found to have VUR. Eight (19.0%) of these were in the ALN group and 26 (16.5%) were in the non-ALN group (p=0.868). The rates of high-grade VUR (grade IV–V) were similar in the two groups (25.0% *vs.* 19.2%; p=0.947). VUR was the most common genitourinary tract anomaly, followed by hydronephrosis (7%). Other anomalies included hydroureter, small kidneys, single kidneys, double orifice of the urethra, and Cobb's collar. The rate of these genitourinary tract anomalies did not differ significantly between the two groups.

Uropathogens and antimicrobial resistance patterns

Two hundred and sixty-one children had a positive urine culture; 234 had a single pathogen, and 27 had mixed pathogens. Two children in each group had a negative culture. These four children had fever and pyuria and all had been pretreated with oral first generation cephalosporin 1–2 days prior to admission. The two children in

Table 2. Comparisons of laboratory and image studies between ALN and non-ALN children[a]

Variable	ALN group ($n=51$)	non-ALN group ($n=214$)	p
WBC ($\times 10^9$/L)	18.86±8.72	15.08±6.53	0.003[c]
Neutrophils (%)	61.4±17.4	52.7±15.2	<0.001[c]
Hemoglobin (g/dL)	10.8±1.1	11.2±1.6	0.05
Platelet count ($10^3/\mu L$)	321±132	358±121	0.143
C-reactive protein (mg/dL)	9.0±6.3	3.5±4.2	<0.001[c]
Urinalysis			
Pyuria (WBC>5/HPF)	50 (98.0)[b]	183 (85.5)	0.026[c]
Hematuria (RBC>5/HPF)	21 (41.2)	74 (34.6)	0.471
Nitrite test	15 (29.4)	61 (28.5)	0.965
VUR[b]	8 (19.0)	26 (16.5)	0.868
Grade I–III	6 (75.0)	21 (80.8)	0.947
Grade IV–V	2 (25.0)	5 (19.2)	0.947
Hydronephrosis	6 (11.8)	12 (5.6)	0.258
Structure anomalies	16 (31.4)	39 (18.2)	0.097

[a]Data presented as mean±standard deviation or *n* (%); [b]VUR was performed in 42 children in ALN group and 158 children in non-ALN group; [c]statistically significant. ALN=acute lobar nephronia; WBC=white blood cell; RBC=red blood cell; HPF=high power field; VUR=vesicoureteral reflux.

the uncomplicated UTI group were found to have VUR on subsequent VCUG examination. *E. coli* was the most common pathogen found in both the ALN and uncomplicated UTI groups (90% *vs.* 79%; $p=0.108$; Table 3). *E. coli* infection with extended-spectrum beta-lactamase (ESBL) was found in two of the ALN children but in none of the uncomplicated UTI children.

The antibiotic resistance patterns of the *E. coli* isolated from children with ALN and uncomplicated UTI are shown in Table 4. Overall, the *E. coli* strains exhibited high antimicrobial resistance to ampicillin (77%), amoxicillin/clavulanic acid (19%) and cotrimoxazole (45%). The *E. coli* isolates from ALN children were more resistant to ciprofloxacin and cotrimoxazole ($p<0.01$) than those from non-ALN children. No suitable oral antibiotic could be found for one child with *E. coli* ALN after defervescence, who was hospitalized for 21 days on intravenous antibiotics.

Discussion

UTIs are very common in febrile children. The differential diagnosis of acute renal inflammatory disease can cause difficulties in pediatric patients, especially in young infants. In 1979, Rosenfield first described ALN with the usual wedge-shaped distribution of inflammation comparable to that seen in lobar pneumonia.[5] Histologically, ALN shows localized hyperemia, interstitial edema and leukocyte infiltration compared with local areas of tissue necrosis and liquefaction seen in renal abscess. It is not a rare condition and it is probably under diagnosed.[10] Therefore, with more awareness and the advancements in noninvasive image modalities, ALN is now being diagnosed with increasing frequency.[7]

In this study, we wanted to know the rate of ALN in previously healthy children hospitalized due to a first episode of community-acquired febrile UTI. Compared with other studies,[7,16] only children without underlying disease were chosen for analysis, and the rate of ALN was found to be high (19.2%). We also found that the mean age (1.86 years) of ALN children was significantly greater than that (0.81 year) of non-ALN children with uncomplicated UTIs. In general, febrile young infants less than 3 months of age are hospitalized for thorough examination. Forty-seven percent of children in the uncomplicated UTI group were less than 3 months of age and were hospitalized within1–2 days of fever. Conversely, older children are more likely to be diagnosed with other febrile illnesses before admission. The specific symptoms of UTI are hard to assess

Table 3. Comparisons of uropathogens between acute lobar nephronia and non-acute lobar nephronia children

	ALN group (n=51)	non-ALN group (n=214)	p
Negative culture	2 (4)[a]	2 (1)	0.351
Positive culture	49 (96)	212 (99)	
Single pathogen	47 (96)	187 (88)	0.181
Mixed pathogen	2 (4)	25 (12)	
Pathogens			
E. coli	46 (90)	188 (79)	0.108
ESBL-*E. coli*	2 (4)	0 (0)	0.048[b]
Klebsiella spp.	1 (2)	21 (9)	0.164
Proteus spp.	2 (4)	9 (4)	0.718
Citrobacter spp.	0 (0)	3 (1)	0.962
Enterobacter cloacae	0 (0)	1 (0.4)	0.397
Enterococcus spp.	1 (2)	13 (6)	0.482
Group B *Streptococcus*	0 (0)	2 (0.8)	0.786
Morganella morganii	1 (2)	0 (0)	0.397

[a]Data presented as *n* (%); [b]statistically significant. ALN=acute lobar nephronia; ESBL=extended spectrum β-lactamase.

Table 4. Comparisons of antimicrobial resistance rate of *E. coli* between acute lobar nephronia and non-acute lobar nephronia children[a]

	ALN group (n=46)	non-ALN group (n=188)	p
Ampicillin	82	76	0.448
Amoxicillin/ clavulanate	23	18	0.622
Cefazolin	20	12	0.243
Cefmetazole	2	2	0.728
Cefotaxime	7	2	0.151
Imipenem	10	0	0.237
Ertapenem	3	0	0.541
Gentamicin	22	11	0.086
Amikacin	2	0.5	0.827
Cefepime	5	0.5	0.168
Ciprofloxacin	27	6	0.009[b]
Ceftazidime	0	3	0.961
Levofloxacin	7	6	0.901
Cotrimoxazole	66	40	0.003[b]

[a]Data presented as percentage; [b]statistically significant. ALN=Acute lobar nephronia.

and fever is the most common symptom of UTI in infants.[17] Thus, diagnosis is often delayed. In our study, those with ALN had a history of more febrile days before admission (4.7 days) and higher peak body temperatures (39.5°C). The laboratory tests (high white cell counts, neutrophil counts and C-reactive protein levels) also indicated a more severe inflammatory process in the kidneys of these children. This suggests that ALN is a progressive and more severe renal parenchyma infection.

The definitive diagnosis of ALN depends on imaging studies. RUS is usually the first method used and is done routinely in children presenting with a first UTI.[14,18] ALN often manifests as a focal renal mass with poorly defined margins on RUS.[18] In contrast, a renal abscess characteristically presents as a central anechoic area with clearly defined margins[7] and the sonography is normal in most cases of acute uncomplicated pyelonephritis.[19] A CT scan is considered to be the most sensitive and specific imaging tool for ALN.[3,16,20] Sonography can detect severe nephromegaly with a sensitivity of 90.0% and specificity of 86.4% compared with the "gold standard" CT scan.[3,16,20] The 51 children with ALN in this study all had nephromegaly either with, or without, a focal renal mass as detected by sonography, and of the 40 who received CT scans, typical image results were found. The confirmation of ALN using CT scan after the finding of nephromegaly on RUS is helpful in practice.[14]

ALN is thought to be caused by an ascending infection from the lower urinary tract, or by hematogenous spread. All blood cultures were negative in the 51 ALN children.

In our study, 22% of children had urologic abnormalities. The most frequent abnormality was VUR, affecting 17% of children, which is similar to that seen in a previous study on children with a first UTI in Taiwan.[11,21] The rate of VUR ranges from 32% to 44% in children with ALN in other studies.[7,8,22] The incidence rate and the severity of VUR were similar between the two groups in our study. This suggests that VUR may not be a prerequisite for ALN.[10]

E. coli was the most common pathogen causing UTIs, including ALN. *E. coli* represents over 90% of the microorganisms found in ALN children in our study. The local guidelines in Taiwan for the antimicrobial therapy of UTIs in children suggest the use of first or second generation cephalosporins plus aminoglycosides, ampicillin or cotrimoxazole.[23] The resistance of *E. coli* to ampicillin and cotrimoxazole has increased over the last decade.[11] Similarly, the *E. coli* in our study showed high resistance to ampicillin (77%) and cotrimoxazole (45%). In contrast, resistance to first or second generation cephalosporins or aminoglycosides was relative low (cefazolin, 14%; cefmetazole, 2%; gentamicin, 13%). Therefore, first generation cephalosporins are an appropriate treatment for pediatric cases of community-acquired UTIs. There were no differences in the antibiotic susceptibility of the *E. coli* isolated in this study, except to ciprofloxacin ($p = 0.009$) and cotrimoxazole ($p = 0.003$), between the two groups. Interestingly, two of the children in the ALN group (4%; $p < 0.05$) had ESBL-*E. coli* infections. The inappropriate empiric antibiotic rates for ALN and non-ALN were 9.8% and 4.7%, respectively. The instances of antibiotic treatments were more frequent than the instances of inappropriate empiric antibiotic treatment. The most common reason for changing antibiotics in the ALN group was persistent fever, after 2 or more days of antibiotic treatment. The main reason for change in the uncomplicated UTI group was the isolation of microbes that were only susceptible to treatment with gentamicin.

The clinical distinction of ALN from other renal parenchymal infections can be difficult, but it is extremely important because the treatment may differ. The treatment of ALN, such as that seen with uncomplicated febrile UTIs, needs only antibiotics. A 3-week treatment with antibiotics is recommended, rather than 10–14 days.[10] In contrast, surgical drainage plus antibiotic treatment may be required for renal abscess. The early identification and prompt treatment of ALN is important to prevent its progression to renal abscess.

ALN is a more severe form of renal parenchyma infection, and the fever lasts longer in spite of effective antibiotic treatment.[22] In this study, it took almost 3 days of antibiotic treatment to bring the fever down. In the same way, there is the need for longer periods of intravenous antibiotic treatment, longer hospital stays and increased medical costs. By understanding the natural course of ALN, there is no need to change antibiotics when a fever is sustained. It is also reasonable to separate ALN from uncomplicated UTIs, or pyelonephritis, if diagnosis related groups are covered by national health insurance.

In conclusion, ALN is not uncommon in previously healthy children with a first episode of febrile UTI, and should be considered as a differential diagnosis of renal parenchyma infection. Children with ALN usually have a prolonged and intractable clinical course as well as laboratory data suggestive of severe inflammation. RUS should be done routinely and CT scan is the most sensitive diagnostic tool for ALN. VUR is common in children with ALN, but not specific for ALN. Also, longer treatments periods with the appropriate antibiotics is recommended for the therapy of ALN.

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